DEPENDENCE OF THE REACTIVITY OF FIVE-MEMBERED AROMATIC HETEROCYCLES ON THEIR STRUCTURE.

1. EFFECT OF THE NUMBER, TYPE, AND POSITION OF NITROGEN ATOMS ON THE PROTON AFFINITY OF AMINOAZOLES

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The proton affinities (PA) of 16 aminoazoles were calculated by the MNDO and ab initio methods. It was assumed that the effect of the heteroatom on the PA is determined by its type and position and does not depend on the presence of other heteroatoms in the ring. Quantitative characteristics reflecting the effect of heteroatoms at various positions on the PA were obtained by the method of least squares.

To a significant degree the study of heterocyclic compounds involves determination of the dependence of the chemical characteristics of a reaction group attached to the ring on the number, type, and position of heteroatoms in the ring. Some of the most widespread reactions include the reactions of amino derivatives of heterocycles with electrophilic reagents (protonation, alkylation, acylation, reactions with carbonyl reagents, etc.).

In this connection we undertook a quantum-chemical investigation into electrophilic attack on a primary amino group situated at a carbon atom in the heterocycle for the case of the simplest electrophile, i.e., the proton. As substituents at the amino group we used five-membered aromatic nitrogen heterocycles (pyrrole, pyrazole, imidazole, triazoles, tetrazole). In accordance with the aim of the work we only investigated protonation at the exocyclic nitrogen atom. As a characteristic of the reactivity we used the proton affinity, which we calculated as the difference between the total energies of the protonated and basic forms of the amines.

The total energies were calculated by a nonempirical method by means of the GAUSSIAN-76 program in the STO-3G minimal basis set. Although this method gives high values for the proton affinity compared with the experimental values [1], there is nevertheless a good linear correlation between them. This was demonstrated for a wide range of neutral molecules and anions during protonation at the C, N, O, F, P, and S atoms [2, 3] and also for protonation at the amino group in cases where the amino group is attached to an aromatic ring [4].

On account of the lack of experimental data on the structures of the investigated compounds, during the calculations we assumed that the atoms of the heterocycles and the nitrogen of the amino group lie in one plane, and we optimized the remaining geometric parameters. Since optimization within the scope of the ab initio method requires large expenditures of computer time, optimization is usually achieved by various semiempirical methods [5]. We used one of the best of such methods, i.e., the MNDO method [6], which gives a geometry close to the experimental geometry [7].

The results from optimization showed that the amino group is pyramidal in all cases; during its rotation about the C–N bond the hydrogen atoms can lie both on one side and on different sides of the plane of the ring.

Table 1 gives the average lengths of the bonds between the atoms for the various positions of these bonds in relation to the amino (ammonium) group. From the table it is seen that both in the protonated molecule and in the unprotonated molecule the lengths of bonds of the same type are approximately the same for the α and γ positions. The bonds at the β position are shorter particularly in the protonated form. In spite of the partial equaliza-

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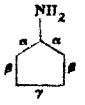
TABLE 1. Bond Lengths in the Aminoazoles, pm



Type of bond	Basic form			Protonated form		
	α	β	γ	α	β	γ
C—N=	140,8±0,7 (0—4)*	139,5±0,6 (0—4)	—	140,0±1,3	138,8±1,2	—
C—NH	139,6±0,6 (8—0)	139,5±0,5 (0—8)	139,6±0,4 (4—0)	140,0±0,9	138,3±0,8	140,2±0,1
C=N	135,5±0,8 (6—2)	134,8±0,9 (2—2)	135,2±0,7 (4—0)	135,7±1,6	134,8±1,0	136,1±0,7
C=C	139,9±0,4 (8—0)	139,4±0,2 (2—0)	139,6±0,1 (2—0)	140,9±0,8	139,8±0,5	140,9±0,4
C—C	144,6±0,1 (0—4)	143,3±0,1 (0—2)	—	143,9±0,6	142,9±0,5	—
=N—N=	—	131,9±0,4 (0—2)	—	—	130,9±0,9	—
N=N	—	126,9±0,1 (0—2)	127,4±0,2 (2—0)	—	126,6±0,3	128,0±0,5
=N—NH	—	133,5±0,8 (0—8)	133,5±0,7 (4—0)	—	132,2±1,3	134,0±0,7

*In the parentheses the number of bonds of the given type which become longer during protonation is given first, and the number of bonds which become shorter is given second.

tion of the lengths of the single and double bonds these bonds nevertheless retain the multiplicity to a significant degree.

In the majority of cases the nature of the change in the bond length during protonation is determined by its type and by its position in the ring, and two trends can be observed. First, the double bonds become longer and the single bonds become shorter during protonation; second, the bond lengths are increased at the α and γ positions and reduced at the β position. Deviations are only observed for the C=N bond at the α and β positions.

In a number of cases these trends do not coincide. The first predominates in the case of the C=C, C—C, and C—N= bonds, and the second in the case of the N—NH, C—NH, and N=N bonds. A tendency for the bond lengths to become equal usually corresponds to an increase in the aromaticity of the heterocycle during protonation. This is evidently explained by the better delocalization of the electron pair of the pyrrole nitrogen atom when the azole ring is attached to an accepting (NH_3^+) and not a π-donating (NH_2) substituent. The increase in the lengths of the bonds at the α position (for the C—NH bonds in particular) may result from an increase in the coulombic repulsion of like-charged atoms in the protonated form. The positive charge at the ring atoms is induced by the NH_3^+ group, and it therefore has the largest value at the close-lying atoms, i.e., at the atoms which form the bonds at the α position. On the other hand, the repulsion of these atoms leads to an increase of 0.65-1.33° in the bond angle at the $C_{(1)}$ atom carrying the substituent (Table 2). This is evidently one of the reasons for the increase in the lengths of the bonds at the γ position.

The ranges of variation of the bond angles in the heterocycles are given in Table 2. The angles at the carbon atoms and at the "pyridine" nitrogen atoms are similar, while the angles for the "pyrrole" nitrogen atoms are somewhat larger. In all the investigated rings the bond angles at the α position increase during protonation while those at the β position decrease. In most cases the angles at the γ position increase (in 27 cases out of 32).

Analysis of the geometric changes which occur during protonation in various parts of the molecule indicates that these changes are determined by the type of fragment (e.g., by the order of the bond and by the nature of the atoms which form it) and also by its position in the ring. However, the direction of variation does not depend on the structure of the other parts of the ring. This is reminiscent of the fact that the effect of various structural fragments on the proton affinity can be mutually independent and determined solely by their form and by their position in the ring.

TABLE 2. Bond Angles in the Heterocycles, deg

Position	C	N	NH
α	103,7—112,8	—	—
	(104,4—114,0)*	—	—
β	102,7—109,8	102,3—109,1	105,3—112,5
	(101,9—109,0)	(101,8—108,4)	(104,6—111,3)
γ	105,8—112,4	104,8—112,6	108,5—115,9
	(105,7—111,5)	(105,9—112,4)	(109,0—116,0)

*The values of the bond angles in the protonated form are given in parentheses.

TABLE 3. Values of the Proton Affinity of Aminoazoles (au), Calculated by the MNDO and STO-3G Methods and from the Correlation Equations (4) and (5)

Position of nitrogen atoms	MNDO	Eq. (5)	STO-3G	Eq. (4)
4-NH	−0,2674	−0,2690	−0,4402	−0,4404
4-NH-3-N	−0,2559	−0,2547	−0,4221	−0,4220
4-NH-5-N	−0,2549	−0,2549	−0,4246	−0,4253
4-NH-2-N	−0,2603	−0,2593	−0,4334	−0,4312
4-NH-2,3-N	−0,2455	−0,2450	−0,4137	−0,4129
4-NH-3,5-N	−0,2411	−0,2406	−0,4079	−0,4069
4-NH-2,5-N	−0,2459	−0,2452	−0,4160	−0,4161
4-NH-2,3,5-N	−0,2288	−0,2309	−0,3951	−0,3979
2-NH	−0,2428	−0,2506	−0,4170	−0,4195
2-NH-3-N	−0,2341	−0,2363	−0,4012	−0,4012
2-NH-5-N	−0,2373	−0,2366	−0,4054	−0,4044
2-NH-4-N	−0,2395	−0,2363	−0,4016	−0,4012
2-NH-3,4-N	−0,2221	−0,2220	−0,3825	−0,3828
2-NH-3,5-N	−0,2212	−0,2223	−0,3880	−0,3861
2-NH-4,5-N	−0,2251	−0,2223	−0,3862	−0,3861
2-NH-3,4,5-N	−0,2068	−0,2080	−0,3675	−0,3677

The proton affinities obtained by the MNDO and STO-3G methods are given in Table 3. Earlier, during assessment of the suitability of the MDNO method for calculation of the proton affinities of amines it was indicated [8] that this method gives incorrect results for alkylamines with variation in the degree of substitution of the nitrogen atom. However, direct changes at the protonation center (the amino group) do not occur in our investigated series, and it can be supposed that it will be correct to use the MNDO method in this case. In fact, comparison of the proton affinities calculated by the MDNO and STO-3G methods showed that there is a linear relation between them with a high correlation coefficient:

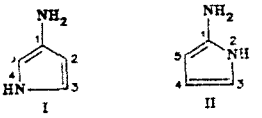
$$PA_{STO\text{-}3G} = 1.195 \cdot PA_{MNDO} - 0.1200 \quad (r = 0.992; \quad S = 0.00245; \quad F = 937). \tag{1}$$

On the basis of the supposed nondependence of the effect of the heteroatoms on the proton affinity for any aminoazole obtained from aminopyrrole (I) by substitution of one or several carbon atoms by the —N= nitrogen atoms or by substitution of the 4-NH fragment by the 2-NH fragment [structure (II)] the proton affinity can be expressed in terms of the equation:

$$PA = PA_0 + n_2\Delta E_2 + n_3\Delta E_3 + n_4\Delta E_4 + n_5\Delta E_5 + n_{NH}\Delta E_{NH}, \tag{2}$$

where PA_0 is the proton affinity of the amine taken as reference point. For this purpose it is convenient to use aminopyrrole (I), which has the largest proton affinity; n_2, n_3, n_4, and n_5 are the numbers of dicoordinated nitrogen atoms at the corresponding positions of the ring; n_{NH} is the number of —NH— groups at position 2; ΔE_2, ΔE_3, ΔE_4, and ΔE_5 are quantities reflecting the effect of the heteroatom at the given positions on the proton affinity;

ΔE_{NH} reflects the change in the proton affinity during the transition from the 4-NH isomer to the 2-NH isomer.



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Of course, Eq. (2) only holds in the case where the ΔE_i values are constant for all the investigated compounds. The ΔE_i and ΔE_{NH} values were determined by the method of least squares, and this led to the following equation:

$$PA_{STO\text{-}3G} = -0.4404 + 0.0092n_2 + 0.0183n_3 + 0.0184n_4 + 0.0151n_5 + 0.0208n_{NH} \quad (r = 0.998; \quad S = 0.0013; \quad F = 449). \quad (3)$$

The high correlation coefficient and the small mean-square deviation indicate that Eq. (3) describes the variation of the proton affinity in the series of aminoazoles well.

It is interesting to compare the effects of heteroatoms at various positions on the proton affinity. It should at once be noted that the introduction of heteroatoms leads to a decrease in the proton affinity in all cases (all $\Delta E_i > 0$). This is not surprising, since nitrogen has a higher electronegativity than carbon. The effect of atoms at the β positions (positions 3 and 4) is practically identical and does not, consequently, depend on the system of bonds and atoms through which it is transmitted. This makes it possible to simplify Eq. (3) by putting $\Delta E_3 = \Delta E_4$. By the method of least squares we obtain the following equations:

$$PA_{STO\text{-}3G} = -0.4404 + 0.0092n_2 + 0.0184(n_3 + n_4) + 0.0151n_5 + 0.0209n_{NH} \quad (r = 0.998; \quad S = 0.0013; \quad F = 617), \quad (4)$$

$$PA_{MNDO} = -0.2690 + 0.0097n_2 + 0.0143(n_3 + n_4) + 0.0141n_5 + 0.0183n_{NH} \quad (r = 0.995; \quad S = 0.0016; \quad F = 269). \quad (5)$$

The ΔE_i values in Eqs. (4) and (5) show identical tendencies for variation, but the correlation with the proton affinities calculated by the MNDO method is somewhat poorer than with the data obtained by the STO-3G method. The proton affinities calculated by means of the correlation equations (4) and (5) are given in Table 3.

The α-nitrogen atoms (positions 2 and 5), unlike the β atoms, differ greatly in their effects on the proton affinity. As already mentioned, full delocalization of the bonds is absent in the ring, and they retain their order to a significant degree. As a result it is found that the α-atoms are attached to the amino group through bonds with different orders. The fact that the effect of the atom at position 2 is approximately 1.5 times weaker than that of the atom at position 5 indicates that the conduction of the effect is stronger through a bond of higher order than through a bond of lower order.

The position of the —NH fragment has a strong effect on the proton affinity. If the amino group is at the α position, its proton affinity is lower than for the amino group at the β position. The result is consistent with the values of the σ constants for the α- and β-pyrrole substituent, according to which β-pyrrolyl is a stronger electron donor than α-pyrrolyl [9].

Thus, it has been shown that the proton affinities of aminoazoles can be calculated with great accuracy by an additive method as a function of the number, type, and position of the heteroatoms in the ring without regard to their mutual effects.

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RESEARCH ON IMIDAZO[1,2-*a*]BENZIMIDAZOLE DERIVATIVES.

23.* SYNTHESES BASED ON 2-(2-HYDROXYETHYLAMINO)BENZIMIDAZOLES

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The possibility of annelation of the imidazoline ring on the basis of 2(2-hydroxyethylamino)-benzimidazoles was studied. It was shown that the action of hydrobromic, sulfuric, nitrosylsulfuric, and polyphosphoric acids, acetic anhydride, and phosphorus oxychloride on them does not lead to 2,3-dihydroimidazo[1,2-*a*]-benzimidazoles. In the case of $POCl_3$ the products were 2-(2-chloroethylamino)benzimidazoles, treatment of which with alcoholic alkali led primarily to nucleophilic substitution of the chlorine atom by a methoxy group. Three-ring imidazolines are formed in 12-15% yields in this case. It was established that the reaction proceeds through the intermediate formation of aziridine derivatives.

The ease of replacement of the sulfo group in benzimidazole-2-sulfonic acids by various amines, including the β-hydroxyethylamino group, was demonstrated in [2]. Considering the fact that derivatives of nitrogen heterocycles that have this sort of group in the α position relative to the nitrogen atom of the heteroatom are convenient synthones in the synthesis of condensed imidazoline systems with a common nitrogen atom, we investigated the possibility of the use of 2-(2-hydroxyethylamino)benzimidazoles I for the synthesis of 2,3-dihydroimidazo[1,2-*a*]benzimidazole derivatives VII.

Attempts to bring about the cyclization of amino alcohols I directly to VII by the action of HBr, H_2SO_4, and nitrosylsulfuric and polyphosphoric acids were unsuccessful (see [3-6]). Sulfonation of the OH group to give acids II occurs as a result of the action of H_2SO_4. Treatment with nitrosylsulfuric acid leads to nitrosoamino sulfonic acid III, which remains unchanged when it is treated with alkali. Acetic anhydride also proved to be an unsuitable reagent for the transition to VII: Its action on amino alcohols Ia,b leads only to acetylation of the amino and hydroxy groups. Bands that characterize the absorption of the NH and OH groups in starting Ib vanish in the IR spectrum of the resulting diacetate IVb, and bands at 1685 and 1735 cm^{-1}, which should be ascribed to the carbonyl absorption of acetamido and acetoxy groups respectively, appear. The same bands are also present in the spectrum of IVa, which was similarly obtained. Two partially overlapped singlets of methyl protons of two acetyl groups at 1.82 and 1.77 ppm are observed in the PMR spectrum of a solution of IVb in $CDCl_3$; the ring $N-CH_3$ group gives a singlet at 3.6 ppm, and the ethylene protons appear in the form of two symmetrical doublets at 4.18 and 4.0 ppm.

Refluxing amino alcohols I in phosphorus oxychloride leads to chlorination of the hydroxy group and the formation of 2-(2-chloroethylamino)benzimidazole hydrochlorides V. The

*See [1] for communication 22.

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